REMARKS

Claim Status

This application contains claims 10-15 and 21-23. Claim 10 has been amended and new claim 23 has been added to more particularly point out and distinctly claim the subject matter that Applicants wish to prosecute in this application. Support for amended claim 10 and new claim 23 may be found, for example, in paragraph [0041] on page 13 of the specification as filed. No new matter has been introduced. Reconsideration is respectfully requested.

Claim Rejection - 35 U.S.C. §103

Claims 10-15, 21 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,866,849 (hereafter "the '849 patent") in view of Ghanta et al., 1996, *J. Biol. Chem.*, 271(47): 29,525-29,528 (hereafter "Ghanta"), U.S. patent no. 6, 962,707 (hereafter "the '707 patent"), and Maillere et al., 1995, *Molecular Immunology*, 32(17/18): 1377-1385 (hereafter "Maillere"). The Examiner states that these documents provide sufficient motivation to combine the teachings of the foregoing references to arrive at the claimed invention with a reasonable expectation of success, and that such a combination teaches each and every limitation of the claims. These grounds for rejection are not well taken and are respectfully traversed.

Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. The '849 patent, Ghanta, the '707 patent, and Maillere do not suggest, alone or in combination, the instant claims because they do not suggest the synthetic amyloid β (hereafter "Aβ") peptides defined by the claims nor that such claims are capable of eliciting a desired immune response.

The peptides called for in the present claims are based upon SEQ ID NO: 1 with the modifications as described:

An isolated peptide comprising the amino acid sequence:

(Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala)$_n$ (SEQ ID NO:1)

wherein n is 1 or 2; and

wherein the isolated peptide further comprises an N-terminal, C-terminal, or both N- and C-terminal, polylysine or polyaspartate sequence of 4-10 residues.

The pending claims encompass Aβ peptides for use as an immunogen to mount an immune response designed to interfere with natural Aβ peptides and amyloid deposits. The inventive peptides have reduced ability to adopt β-sheet conformation as an antigenic source and have a lower risk of leading to any toxic effects in humans.

The Examiner relies upon the '849 patent as the primary reference for his obviousness rejection. As Applicants stated in their November 21, 2006 Response, the '849 patent discloses administration of a peptide consisting of the first 39 amino acids of natural amyloid β (hereafter "Aβ1-39") for evoking a therapeutic antibody response. The Examiner acknowledges that the '849 patent is silent regarding any modifications to the natural Aβ1-39 fragment. Moreover, Applicants assert that the '849 patent does not teach or suggest the synthetic Aβ peptides defined by the instant claims as described above.

The Examiner attempts to cure the deficiencies of the '849 patent with Ghanta. However, nothing in Ghanta, alone or in combination with the '849 patent, suggests or teaches Applicants' peptides as defined by the present claims. The Examiner states on page 2 of the February 23, 2007 Office Action "that Ghanta cited earlier work to teach that the unmodified N-terminal peptide of Aβ forms neurotoxic aggregates" and on page 3 of the February 23, 2007 Office Action "that Ghanta is relied upon to suggest modification of the Aβ N-terminal peptide with lysine hexamers to reduce neurotoxicity associated with the unmodified N-terminal of Aβ."

In contrast to the Examiner's characterization, the peptides taught by Ghanta are distinguishable from the claimed peptides for at least two reasons: 1) the Ghanta peptides are

internal peptide fragments of Aβ, not an N-terminal Aβ peptide fragment and 2) the peptides in Ghanta are inhibitors that specifically bind to Aβ, not immunogens.

The claimed Aβ peptides are distinguishable from the Ghanta peptides because the claimed Aβ peptides comprise amino acids 1-30 of the N-terminus of the full length Aβ sequence. Ghanta does not disclose or suggest an N-terminal Aβ peptide as called for in the present claims. Instead, Ghanta teaches modification of a peptide consisting of amino acids from the interior of the full-length Aβ sequence. That is to say, the Ghanta peptides comprise amino acids from the internal (not the N-terminal or C-terminal) portion of the full length Aβ. A skilled worker would not have been motivated by an inhibitor consisting of an internal sequence of full length Aβ, to make or use the claimed peptides comprising the N-terminus of full length Aβ.

To illustrate the fundamental difference between the peptides taught by Ghanta and the claimed peptides, Applicants refer the Examiner to the below alignment of the core structure of the peptides:

Full length Aβ (42 amino acid residues):

1 42

N-terminal fragment of Aβ claimed by current invention (30 amino acid residues):

1 30

Internal fragment of Aβ taught by Ghanta (10 amino acid residues):

15 25

The peptide fragments illustrated above clearly show that the 10 amino acid peptide taught by Ghanta is not the same as the peptides of the current invention.

There are additional differences between the claimed Aβ peptides and the peptides disclosed in Ghanta. Specifically, in Figure 1 Ghanta describes an exemplary inhibitor peptide consisting of a recognition element of internal amino acids 15-25 of Aβ (hereafter "Aβ15-25") with glycine spacers, an aminocaproate linker, and six lysine residues at the C-terminus of the internal amino acids Aβ15-25 sequence (referred to in Ghanta, and hereafter, as H2). In Figure 1, Ghanta describes another inhibitor consisting of a recognition element of internal amino acids Aβ15-25 with

glycine spacers and six lysine residues at the N-terminus of the internal amino acids Aβ15-25 sequence (referred to in Ghanta as H1). Aβ peptide fragments comprising internal amino acids of full-length Aβ are not the same as fragments comprising the N-terminus 1-30 amino acids of full length Aβ.

A skilled worker would not have been motivated by Ghanta's teachings (pertaining to an internal amino acid sequence) to prepare the peptide defined by the present claims, which has an amino acid sequence with elements that do not correspond to the sequences disclosed in Ghanta. In fact, a skilled worker would not have been motivated by an inhibitor consisting of an internal sequence of full length Aβ, to make or use the claimed peptides comprising the N-terminus of full length Aβ. Thus, the present claims call for an N-terminal Aβ1-30 fragment (either one fragment of 30 amino acids, or two fragments of 60 amino acids), and these sequences are not suggested or disclosed in Ghanta.

The Examiner states in the February 23, 2007 Office Action, on page 3, lines 4-7 that Ghanta is not relied upon for teaching different or longer sequences of amino acids from Aβ than the 10 amino acid sequences H1 and H2. Applicants in their November 21, 2006 Response stated that Ghanta does not teach or suggest using a different or longer sequence of amino acids from Aβ than the 10 amino acid fragments described as H1 and H2. If anything, Ghanta states that shorter peptide sequences, D-amino acid sequences, or organic peptidomimetics could serve as recognition elements in place of Aβ15-25 (See Ghanta, page 29528, column 2). This is hardly a suggestion that would lead one of ordinary skill to create a longer peptide comprising the N-terminal of Aβ as claimed.

The second reason that the claimed Aβ peptides are distinguishable from the Ghanta peptides is because the claimed Aβ peptides are immunogens, not inhibitors. As stated on page 11, paragraph [0036] of the specification, as filed, the claimed peptides have "a reduced ability to adopt a β-sheet conformation as an antigenic source but also would have a much lower risk of leading to any toxic effects in humans." The last sentence of paragraph [0036] of the specification states "[a]n important object of the present invention is therefore to provide a method for immunization which minimizes the toxicity associated with injected Aβ peptides while maximizing the immune response

to Aβ peptides and amyloid deposits." In contrast, the peptides disclosed by Ghanta were designed to act as inhibitors of Aβ toxicity by altering Aβ self-assembly. Specifically, Ghanta teaches Aβ peptide inhibitors comprising lysine hexamers that bind to Aβ and act as disrupting elements that alter the self-assembly of Aβ, thereby ameliorating the toxicity of Aβ. *See* Ghanta on page 29525, second column, third full paragraph, sentences 3-5. Ghanta does not describe or suggest use of the inhibitor fragments as immunogens. Importantly, the skilled worker would have no reasonable expectation that an inhibitor may be used successfully as an immunogen. For this reason, and contrary to the Examiner's statement, a skilled worker would not reasonably expect that the net benefit of the combined methods of the '849 patent and Ghanta would be greater than that taught in the '849 patent. In fact, as discussed above, there would have been no motivation for a skilled worker to use the inhibitor, as modified by Ghanta, as an immunogen to arrive at the present claims. Thus, Ghanta fails to cure the deficiencies of the '849 patent.

The Examiner cites the '707 patent as demonstrating the success a skilled worker would expect if he combined the teachings of the '849 patent with the teachings of Ghanta. The '707 patent discloses a therapeutic agent comprising polylysine or polyglutamic acid linked to the amino or carboxyl terminus of an immunogenic, natural Aβ peptide. The Examiner acknowledges that the '707 patent does not teach polyaspartate of the 4-10 amino acid limitations taught by Applicants. However, the Examiner concludes that the '707 patent indicates that the "addition of polyamino acids to Aβ peptide immunogen is potentially beneficial and at least feasible." Applicants respectfully disagree with the Examiner's statements regarding Applicants' invention in light of the '707 patent.

As discussed above, because neither the '849 patent nor Ghanta describes or suggests Applicants' claimed peptides, the '707 patent cannot demonstrate the success a skilled worker would expect if he combined the '849 patent and Ghanta. Furthermore, the '707 patent does not cure the deficiencies of the '849 patent and Ghanta.

The Examiner cites Maillere as allegedly teaching that amidation of the C-terminus of an administered peptide decreases proteolytic degradation of peptides, thereby enhancing the capacity of the peptide to activate lymphocytes. Based upon Maillere, the Examiner states that "the skilled

artisan seeking to evoke an immune response to Aβ peptides would expect that C-terminal amidation would be an advantageous modification." Applicants respectfully disagree.

The Examiner attempts to cure the deficiencies of the '849 patent, Ghanta, and the '707 patent with Maillere. However, nothing in Maillere, alone or in combination with the '849 patent, Ghanta, or the '707 patent describes or suggests Applicants' claimed peptides.

As discussed above, Applicants provide reasons why one of ordinary skill in the art, even if so motivated, would not have been able to predict the success of combining the claimed elements to successfully arrive upon the Aβ peptides as claimed. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The difficulties described above indicate that a likelihood of success for creating the claimed Aβ peptides would not be found in the prior art.

At best, the cited references provide only an invitation to experiment further, which is insufficient to establish obviousness in the context of unpredictable results. Determining the various elements that can be combined to make a peptide suitable as an immunogen to elicit a desired immune response requires experimentation and is unpredictable until a peptide of that type is made and tested. It was only through experiments carried out by the present inventors as described in the specification that the parameters for the inventive peptides were determined and tested. MPEP § 2145(X)(B); *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988); *see also Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000) ("'obvious to try' is not the standard"). Finally, this conclusion is consistent with the recent Supreme Court decision *KSR v. Teleflex*, 550 U.S.___ (2007)[1] where in contrast to the presently claimed peptides, the court discussed *predictable* outcomes that support a finding of obviousness stating:

> The combination of familiar elements according to known methods is *likely to be obvious when it does no more than yield predictable results.*" (emphasis added) (discussing *United States v. Adams*, 383 U.S. 39, 40 (1966) (the companion case to

[1] Holding that *Graham v. John Deere* controls the obviousness inquiry and warning that a rigid application of the teaching / suggestion / motivation test as a litmus test for obviousness is inconsistent with the *Graham* framework.

Graham), *Anderson's Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

Assembling the claimed elements in the manner discovered by the inventors was not a mere combination that yielded predictable results.

For at least the reasons set forth above, pending claims 10-15, 21, and 22, as well as new claim 23, are not obvious over the prior art of record. Reconsideration of the claims and withdrawal of the rejections under 35 U.S.C.§ 103(a) is respectfully requested.

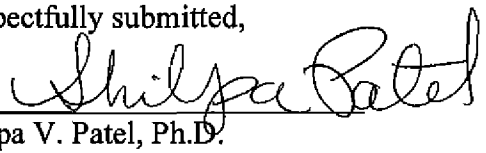
CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: August 22, 2007

Respectfully submitted,

By 

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